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EXAMINER	
SHAFER, SHULAMITH H	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 06/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/630,227	DIMAURO ET AL.	
	Examiner	Art Unit	
	Shulamith H. Shafer, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,14,34,36-51,53-65 and 84-92* is/are pending in the application.

4a) Of the above claim(s) *84-88* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,14,34,36-51,53-65 and 89-92* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/13/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

Status of Application, Amendments, And/Or Claims:

The amendment received 4 April 2006 in response to the Office Action of 4 January 2006 has been entered. Claims 1, 2, 14, 34, 36-51, 53-65 are now pending. Claim 62 was inadvertently withdrawn in the Office Action of 4 January 2006, but is now under examination as being drawn to the elected invention. Claims 1, 34, 68, 48, 51, 55, 63, and 65 have been amended and the amendments have been entered. Claims 14, 44, and 59 have been cancelled at applicants request. New claims 84-92 have been added and entered. The pertinent remarks/arguments filed with the amendment received 4 April 2006 will be responded to herein.

The text of those sections of Title 35 U.S. Code not included in this action can be found in the prior Office action.

New claims 84-92 have been added. Claims 84-88 are drawn to "a method of treating an inflamed orthopedic joint, wherein the inflammation of the orthopedic joint results in ankylosing spondylitis .....comprising trans-capsularly administering into the joint space a formulation comprising an effective amount of an inhibitor of TNF-α synthesis...". Claim 85 recites "wherein said inhibitor of TNF-α synthesis is infliximab"; Claim 86 recites "wherein said inhibitor of TNF-α synthesis is adalimulab". Claim 87 recites "wherein said inhibitor of TNF-α synthesis is CDP-571". Claim 88 recites "wherein said inhibitor of TNF-α synthesis is CDP-870". These claims are drawn to an invention other than the one initially elected by applicants. Applicants' original election was drawn to a method of treating an inflamed orthopedic joint. In response to requirement for species election, applicants had elected: (a) High specificity antagonist – Inhibitor of TNF-α synthesis; (b) Type of joint – Knee joint; (c) Additional agent – growth factor. One of ordinary skill in the art would not recognize that "inflammation of the orthopedic joint results in ankylosing spondylitis". Ankylosing spondyliltis is generally recognized to be a form of chronic inflammation of the spine and the sacroiliac joints. While ankylosing spondylitis may cause inflammation in or injury to other joints

away from the spine, the art does not recognize inflammation of the joint, such as a knee joint as a causal factor of ankylosing spondylitis (www.medicinenet.com, downloaded 20 June 2006). Therefore, one of ordinary skill in the art would not recognize inflammation of the knee joint as causing ankylosing spondylitis.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 84-88 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 1, 2, 34, 36-43, 44-51, 53-58, 60-65, and 90-92 are under examination to the extent that they read on the elected invention.

Objections/Rejections Withdrawn

The objection to claims 14, 44 and 59 as encompassing non-elected inventions has been rendered moot by cancellation of the claims.

The objection to Claim 59 because of the following informalities: Claim 59 is a duplicate of Claim 38 has been rendered moot by cancellation of the claim.

The objection to Claims 1, 2, 34, 36-43, 45-51, 53-58 and 60-65 as encompassing non-elected inventions is withdrawn in view of applicants' amendments to claims 1, 38, 48, 51, 55, 63 and 65.

The rejection of claims 14, 44 and 59 under 35 U.S.C. 112, second paragraph has been rendered moot by cancellation of the claims.

The rejection of claims 44 and 59 under 35 U.S.C. § 112, First Paragraph, has been rendered moot by cancellation of the claims.

The rejection of claims 1, 2, 34, 36-43, 45-51, 53-58, 60-65 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention because the method steps does not match the goal set forth in the preamble, and the recitation of "effective

amount" and "high specificity antagonist" in claim 1 is withdrawn in view of applicants' amendment to Claim 1.

The rejection of Claim 14 under 35 U.S.C. 103 (a) as being unpatentable over Lehman et al (2002, J Pediatric 140:125-7) in view of Dunn (2001, EP 1 153 607) has been rendered moot by cancellation of the claim.

Maintained Rejections/New Grounds for Rejection

35 U.S.C. § 112, Second Paragraph:

The rejection of Claims 38 and 48 under 35 U.S.C., second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained for reasons of record (Office Action of 4 January 2006) and for reasons outlined below.

Applicants traverse this requirement on the grounds that the claims, as now amended recite administration of "an inhibitor of TNF-α synthesis" rather than a high specificity antagonist; therefore, the claims, as amended would allow one of ordinary skill in the art to understand what is meant by an inhibitor of TNF-α synthesis present in the formulation in an amount of at least 100 mg/ml (Claim 38) and present in the formulation in a maximum amount of 0.5 mg (Claim 48). Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons. Applicants disclose a large number of compounds that prevent and/or inhibit TNF synthesis (page 15, lines 20-29). These compounds are a non-limiting list and include compounds of vastly different chemical structures, functions, size and molecular weights. Claim 1, the independent claim of the instant invention, recites the limitation of "administering .....a formulation comprising an effective amount of an inhibitor of TNF-α synthesis". Since the disclosure teaches a myriad of compounds of vastly different molecular weights and sizes and does not identify a specific structure, the recitation of specific dosages are meaningless.

35 U.S.C. § 112, First Paragraph:

The rejection of Claim(s) 38, 46, and 48 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is maintained for reasons of record (Office Action of 4 January 2006) and for reasons set forth below. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants traverse this rejection as applied to claim 46 on the following grounds:

1. Although LaVan et al. (cited by examiner in Office Action of 4 January 2006) discloses that there are stability problems with in vivo glucose sensors, the reference does not teach any such problems with a sustained release device that comprises an inflammatory-responsive delivery system.

2. Pike et al (cited by examiner in Office Action of 4 January 2006) state that a sustained release device comprising inflammatory-responsive delivery systems is "well known in the art" and can be used to administer a therapeutically effective dose of an agent directly at the site.

Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons. The specification provides no guidance and/or direction or working examples of a sustained release device which could deliver a formulation comprising an effective amount of an inhibitor of TNF-α synthesis wherein the sustained release devise comprises an inflammatory-responsive delivery system (claim 46); the only mention of a device with such limitations is in the recitation of the claims. The teachings in the art do not remedy this lack of guidance in the disclosure. LaVan et al (2003, Nature Biotechnology 21:1184-1189) teach that a long-term goal of *in vivo* drug delivery is to couple smart drug delivery devices to other implants, such as biosensors. The reference teaches that a limiting step in the creation of feedback-

controlled drug delivery systems has been the development of stable sensors (page 1189, column 1, 2nd paragraph). LaVan et al. state that many of these "smart" delivery systems still require thorough testing to evaluate both safety and efficacy before clinical use (page 1189, 1st column, last paragraph bridging 2nd column, 1st paragraph). LeVan et al. cite, by way of example, the state of the art which teaches problems in the development of glucose sensors. The reference is silent as to the possibility of the development of "inflammatory responsive delivery system". One could logically conclude that these systems are not yet reduced to practice. Pike et al, in paragraph 0053 (cited by applicants in Remarks of 4 April 2006), teach that sustained-release device or delivery systems are well known in the art, and disclose a biodegradable matrix comprising a therapeutically effective dose of IGF-1 released to maintain therapeutically effective level of IGF-1 at afflicted joint. The reference is silent as to the art as it pertains to a "inflammatory-responsive delivery system".

Applicants traverse the rejection of Claims 38 and 48 under 35 U.S.C. 112, first paragraph as applied to claim 46 on the following grounds:

The amended Claims 38 and 48 now recite that the high specificity antagonist is an inhibitor of TNF-α synthesis; therefore, one of skill in the art could easily determine how to measure an inhibitor of TNF-α synthesis in a formulation in an amount of at least 100 mg/ml or in a formulation in an amount of a maximum amount of 0.5 mg without undue experimentation. Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons. Applicants disclose a large number of compounds that prevent and/or inhibit TNF synthesis (page 15, lines 20-29). This disclosure encompasses a non-limiting variety of compounds and includes compounds of vastly different chemical structures, functions, size and molecular weights. No specific compound or structure is recited, even as an exemplary compound. Since the disclosure teaches a myriad of compounds of vastly different molecular weights and sizes and does not identify a specific structure, the recitation of specific dosages are meaningless. In the absence of a specific recited structure, the skilled artisan is unable to make and or use the compounds recited in claims 38 and 48 without undue

experimentation to find an effective amount, a limitation required by claim 1.

Claim 49 and newly submitted claims 91 and 92 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)).

The claims recite wherein the formulation comprises a growth factor (Claim 49), wherein the growth factor is a bone morphogenetic protein (Claim 91) and wherein the growth factor is a growth and differentiation factor (Claim 92). The specification teaches that the term "growth factors" encompasses any cellular product that modulates the growth or differentiation of other cells" (page 32, lines 11-12). The disclosure asserts that growth factors that may be used include, but are not limited to members of the fibroblast growth factor family, members of the platelet derived growth factor family, EGFs, the TGF-β superfamily, OIF, angiogenins, endothelins, hepatocyte growth factor, keratinocyte growth factor, members of the bone morphogenetic proteins, growth differentiation factors, members of the hedgehog family of proteins, ADMP-1, members of the interleukin family, members of the CSF family and VEGF (page 32, lines 14-26). However, the skilled artisan would be unable to predict which of the recited growth

factors would be useful in the treatment of joint inflammation. Applicants have listed many different families of growth factors, each comprising a number of member proteins. The specification teaches and the art recognizes many members of the BMP family of proteins, each with unique morphogenic effects including, as taught in the specification, BMP-1, BMP-2, BMP-3, OP-1, BMP-2A, BMP-2B and BMP-7. There are also numerous GDFs considered to be a subset of BMP family of proteins.

The relevant literature reports examples of polypeptide families of growth factors wherein individual members have distinct, and sometimes even opposite, biological activities. For example, Tischer et al. (U.S. Patent 5,194,596) establishes that VEGF (a member of the PDGF, or platelet-derived growth factor, family) is mitogenic for vascular endothelial cells but not for vascular smooth muscle cells, which is opposite to the mitogenic activity of naturally occurring PDGF which is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells (column 2, line 46 to column 3, line 2). The differences between PDGF and VEGF are also seen *in vivo*, wherein endothelial-pericyte associations in the eye are disrupted by intraocular administration of PDGF but accelerated by intraocular administration of VEGF (Benjamin et al., 1998, Development 125:1591-1598; see Abstract and pp. 1594-1596). In the transforming growth factor (TGF) family, Vukicevic et al. (1996, PNAS USA 93:9021-9026) disclose that OP-1, a bone morphogenic protein that is a member of the TGF-family of proteins, has the ability to induce metanephrogenesis, whereas closely related TGF-family members BMP-2 and TGF- 1 had no effect on metanephrogenesis under identical conditions (p. 9023, paragraph bridging columns 1-2).

Therefore, based on the discussion above concerning the specific examples of members of the same protein family having proteins that have different functions, along with the art's recognition that one cannot rely upon structural similarity alone to determine functionality, the specification fails to teach the skilled artisan how to use the growth factors, bone morphogenetic proteins or growth differentiation factors in the methods of the claimed invention without resorting to undue experimentation to determine whether a given protein would be useful in treatment of an inflamed joint, and what the appropriate dosage would be.

Due to the large quantity of experimentation necessary to determine which member of a given growth factor family would have the required activity of treating an inflamed joint, the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art establishing that biological activity cannot be predicted based on structural similarity or membership in a given protein family, and the breadth of the claims which embrace a broad class of protein families undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claims 49, 90 and 91 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The claims recite a formulation further comprising "a growth factor present in an amount effective to repair joint tissue" (Claim 49), "wherein the growth factor is a bone morphogenetic protein" (Claim 91) and "wherein the growth factor is a growth differentiation factor" (Claim 92).

The claimed subject matter must be described in the specification to ensure that applicant had in his possession, as of the filing of the application, the specific subject matter claimed. A disclosure in an application, to be complete, must contain such description and details as to enable any person skilled in the art or science to which the invention pertains to make and use the invention as of its filing date.

The skilled artisan would know that there are many different compounds which classified under the heading of "growth factors", BMPs and GDFs. The specification (page 16, line 20) lists a myriad of growth factors that may be used including, but not limited to members of the fibroblast growth factor family, members of the platelet derived growth factor family, EGFs, the TGF-β superfamily, OIF, angiogenins, endothelins, hepatocyte growth factor, keratinocyte growth factor, members of the bone

morphogenetic proteins, growth differentiation factors, members of the hedgehog family of proteins, ADMP-1, members of the interleukin family, members of the CSF family and VEGF (page 32, lines 14-26). Many members of the BMP family of proteins, each with unique morphogenic effects are taught by in the specification, BMP-1, BMP-2, BMP-3, OP-1, BMP-2A, BMP-2B and BMP-7, as well as numerous GDFs, considered to be a subset of BMP family of proteins. Thus, recitation of the large lists of a variety of growth factors is not sufficient to show that Applicant was in possession of the invention, as claimed, but rather, is merely an invitation for further experimentation.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purpose of the 'written description' requirement, whatever is now claimed." (See p. 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is now claimed." (See *Vas-Cath,* at 1116). As discussed above, the skilled artisan cannot envision all of the encompassed growth factors, BMPs and GDFs. Adequate written description requires more than a mere statement that it is part of the invention and reference to a few exemplary compounds.

Therefore, the claimed genus encompassing growth factors, BMPs and GDFs does not meet the written description provision of 35 U.S.C. 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see p. 1115).

Newly submitted Claim 90 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a **new matter** rejection. The claim recites "The method of Claim 1 wherein said inhibitor of TNF-α synthesis is not thalidomide". The specification teaches that compounds which prevent and/or inhibit TNF synthesis include thalidomide, among other recited compounds. Nowhere in the specification is there support for the limitation of excluding thalidomide from the

category of inhibitor of TNF-α synthesis. Thus, the introduction of this limitation in Claim 90 constitutes the introduction of new matter.

35 U.S.C. § 103

The rejection of claims 1, 2, 34, 37, 47, 49, 51, 54 and 56 under 35 U.S.C. 103 (a) as being unpatentable over Lehman et al (2002, J Pediatric 140:125-7) in view of Dunn (2001, EP 1 153 607) is maintained for reasons of record (Office Action of 4 January 2006) and for reasons outlined below.

Applicants traverse this rejection on the grounds that:

1. Lehman et al. teaches that thalidomide has been shown to have both stimulatory and inhibitory effects on TNF-α activity.
2. Lehman et al. do not teach or suggest administration via trans-capsular injection.
3. Lehman et al do not teach or suggest treating an inflamed orthopedic joint with an inhibitor of TNF-α activity.
4. Dunn does not describe or suggest administration of an inhibitor of TNF-α activity
5. One would not be motivated to combine the teachings of Lehman et al. and Dunn with any reasonable expectation of success.

Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Lehman et al. teach the use of thalidomide therapy for recalcitrant systemic onset

juvenile arthritis. The reference teaches that the patients had arthritis in the knees (page 125, column 2, 2nd paragraph and page 126, column 1, three lines from the bottom-bottom of page), a condition involving inflamed orthopedic joints. Lehman et al disclose that thalidomide enhances the degradation of TNF-α mRNA (page 126, column 3, last paragraph) thereby inhibiting the synthesis of TNF-α, a proinflammatory cytokine. Lehman et al do teach that thalidomide was effective because of several factors, including effects on TNF-α (page 126, column 3, last paragraph). The Gori reference is cited by Lehman et al and the applicants to indicate that thalidomide has been shown to have both stimulatory and inhibitory effects on TNF-α activity. However, Gori et al teach administration to a population of HIV- and M. turberculosis-infected patients. The relevance of the Gori teachings to treatment of inflammatory joints is unclear. Furthermore, applicants arguments are inconsistent. Applicants, in Remarks of 4 April 2006 (page 19, 2nd paragraph), argue that thalidomide is not an inhibitor of TNF-α synthesis whereas the specification teaches that thalidomide is among the compounds which prevent and/or inhibit TNF synthesis (page 15, line 22 of specification). Additionally, the preponderance of the Art teaches that thalidomide selectively inhibits TNF-α production (Sampaio et al. 1991. J Exp Med. 173:699-703, abstract; 1999. Muller, GW et al. Biorganic and Medicinal Chem Lett 9:1625-1630, page 1625, 2nd paragraph; 2005. Teo SK. AAPS Journal 7:Article 3, abstract), most likely by enhancing mRNA degradation (1993. Moreira, et al. J Exp Med. 177:1675-1680, page 1678, Figure 4). Therefore, absent evidence to the contrary, Lehman et al. teach administration of an inhibitor of TNF-α synthesis to treat an inflamed orthopedic joint. Lehman does not teach transcapsular administration of the formulation into the knee joint, the transcapsular administration of an inhibitor of the production of the cytokine TNF-α, the transcapsular administration of an additional therapeutic agent, the administration of a formulation of less than 1 cc, the administration of the formulation closely adjacent to the outer wall of the capsule, the administration of a growth factor in an amount effective to repair joint tissue, the administration of a formulation that includes a viscosupplement and the administration performed through a needle. Dunn teaches the injection of a mixture of purified growth hormone and buffer solution into the

joint (abstract, page 1), to treat inflammation of a joint, and specifically discloses treatment of a knee joint (column 1, 0001, line 5-7). The reference teaches the injection of a group of agents such as anti-cytokines (column 3, 0008, lines 45-47), which would by definition include an inhibitor of TNF- α synthesis. Dunn discloses that the method may include an additional step of mixing Lidocaine (an additional therapeutic agent) with the mixture of growth hormone and buffer (Column 4, 0012, lines 11-14), that a preferred volume is generally between 0.5 to 10 milliliters (column 8, 0029, lines 39-40) and that the formulation is injected utilizing a syringe into the joint space and not directly into the bone or tissue (column 7, 0027, lines 30-32, and figure 2). The reference teaches that the invention may additionally comprise the use of a lubricant or viscosupplement such as purified hyaluronic acid or hyaluronate salt (column 9, 0032, lines 25-28). Dunn teaches the administration of a dose of growth hormone as a means of regenerating articular cartilage in the joint, thus achieving repair of joint tissue. It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the formulation comprising thalidomide taught by Lehman using the administration route taught by Dunn. The person of ordinary skill in the art would have been motivated to make that modification because the art recognizes the toxic side effects of the systemic use of thalidomide and Dunn discloses administration of therapeutic agents directly to the joint and a preliminary step involving treatment of the joint with "a group of agents such as anti-cytokines, ...so as to reduce or remove deleterious activity in the joint" (column 3, 0009, lines 38-44). The skilled artisan reasonably would have expected success because Dunn discloses the injection of therapeutic agents into the joint to treat joint inflammation (page 1, abstract).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Dunn teaches

injection of agents such as anti-cytokines to a joint to undergo treatment for inflammation (column 8, 0030, lines 41-48).

Claim 90 is rejected as reciting new matter. If the new matter issue were resolved, Claim 90 would be included in this rejection.

The rejection of Claims 36, 39-43, 45, 58, 60-65 under 35 U.S.C. 103 (a) as being unpatentable over Lehman et al in view of Pike et al. (2003, US PG PUB 2003/0134792) is maintained.

Applicants traverse this rejection on the grounds that:

1. Lehman et al. teach away from administration of an inhibitor of TNF-α synthesis, as thalidomide has been shown to have both stimulatory and inhibitory effects on TNF-α activity
2. Lehman et al. do not teach or suggest administration via trans-capsular injection.
3. Lehman et al do not teach or suggest treating an inflamed orthopedic joint with an inhibitor of TNF-α activity
4. Pike et al. do not teach or suggest administering an inhibitor of TNF-α synthesis
5. One would not be motivated to combine the teachings of Lehman et al. and Pike et al. with any reasonable expectation of success.

Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

The teachings of Lehman et al. and the relevance of these teachings to the

instant application are disclosed in detail above. Lehman et al do not disclose a formulation further comprising liposomes, a sustained, controlled release device, providing continuous release, or intermittent release, a hydrogel, a formulation administered in a volume of between 0.03 and 0.3 ml (30-300 µl), a formulation in a patch attached to an outer wall of the capsule, a formulation in a depot closely adjacent an outer wall of the capsule, a formulation in a depot at a location closely adjacent to an endplate of an adjacent bony body, the release of the antagonist by diffusion through a sustained delivery device, a polymer sustained delivery device, microspheres having a plurality of degradation rates or wherein the antagonist is released by biodegradation of a sustained delivery device. Pike et al disclose a method for treating articular cartilage disorders, including trauma-related cartilage disorders (which would result in inflammation of the joint) such as disorders of the knee (paragraph 0059), by administering IGF-1. Pike et al teach administration of a therapeutically effective dose directly at the site with a sustained release device (paragraph 0053), which would, by definition, comprise a controlled release device providing continuous release. The reference teaches that the device may be implanted within the diseased or injured joint (paragraph 0053), which could encompass attachment to the outer wall of the capsule, or a depot closely adjacent to an outer wall of the capsule or at a location closely adjacent to an endplate of an adjacent bony body. Pike et al teach the formulation may be enclosed in a semipermeable matrix of hydrophobic polymers (paragraph 0044), which would allow for diffusion for the high specificity antagonist through a sustained delivery system (paragraph 0044). The reference teaches the use of hydrogels and microcapsules (paragraph 0044) made of different materials, which would inherently have a plurality of degradation rates and comprise a device which provides intermittent release (paragraph 0044). Pike et al also teach that sustained release forms could include a colloidal drug delivery systems such as liposomes (paragraph 0044). Pike et al teach administration of a pharmaceutical composition in a volume ranging from 100 µl to about 5 ml (paragraph 0047). The reference also discloses the release of a therapeutically effective level of IGF-1 as the matrix degrades (paragraph 0053). It would have been obvious to the person of ordinary skill in the art at the time the

invention was made to modify the formulation comprising thalidomide, an inhibitor of the production of the cytokine TNF-α, as taught by Lehman, by using the delivery systems disclosed by Pike et al. The person of ordinary skill in the art would have been motivated to make that modification because the art recognizes the toxic side effects of the systemic use of thalidomide and Pike et al. teach administration of therapeutic agents directly to administration of therapeutic agents directly to the joint and that the pharmaceutical composition of the disclosed invention may comprise one or more other therapeutic agents including but not limited to anti-inflammatory agents (paragraph 0038), which would include an inhibitor of TNF-α synthesis. The skilled artisan reasonably would have expected success because Pike et al. teach that sustained release devices are well known in the art (paragraph 0053).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Pike teaches the use of sustained release devices applied directly to the joint comprising pharmaceutical compositions of anti-inflammatory agents as treatment for inflammation.

Claim 50 is rejected under 35 U.S.C. 103 (a) as being unpatentable over Lehman et al, and Dunn as applied to Claims 1 and 49 and Molloy et al. (2003, Sports Med 33:381-394).

Applicants traverse this rejection on the grounds that:

1. Lehman et al. teach away from administration of an inhibitor of TNF-α synthesis, as thalidomide has been shown to have both stimulatory and inhibitory effects on TNF-α activity

2. Lehman et al. do not teach or suggest administration via trans-capsular

injection.

3. Lehman et al do not teach or suggest treating an inflamed orthopedic joint with an inhibitor of TNF-α activity

4. Lehman et al. and Dunn do not suggest providing the growth factor by platelet concentration.

5. Molloy et al. teach that PDGF plays a role in tendon healing.

6. One would not be motivated to combine the teachings listed above with any reasonable expectation of success.

Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

The teachings of Lehman et al., and Dunn and the relevance of these teachings to the instant application are disclosed in detail above. Lehman et al., and Dunn do not teach the specific use of a formulation comprising a growth factor derived from platelet concentrate. Dunn et al teach placement of growth factor into the knee. Molloy et al teach that PDGF plays a significant role in early stages of healing of all tendons, both intrasynovial and extrasynovial (page 383, column 1, 1st paragraph and page 387, Column 1, Section 1.4, paragraph 1). Injury to an intrasynovial tendon would, by definition, result in an inflamed orthopedic joint. The reference teaches that the introduction of PDGF into the injury site of healing rabbit femur-MCL-tibia complexes increases the quality of healing (page 390, column 1, paragraph 2 and Table III). It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify a formulation comprising thalidomide, as taught by Lehman by adding a growth factor such as PDGF as suggested by Dunn and Molloy et al. The person of ordinary skill in the art would have been motivated to make that modification because the art recognizes the toxic side effects of the systemic use of

thalidomide, and Dunn teaches delivery of therapeutic compositions directly to the joint and that the composition may comprise one or more additional therapeutic agents including but not limited to anti-inflammatory agents or growth factors and Molloy et al. teach that PDGF has vital functions during early and intermediate stages of healing (page 391, column 2, 2nd paragraph). The skilled artisan reasonably would have expected success because Molloy et al. teach that growth factors have vital functions during early and intermediate stages of healing (page 391, column 2, 2nd paragraph) and Dunn teaches administration of pharmaceutical composition directly to the joint and the disclosed invention may comprise one or more therapeutic agents including but not limited to anti-inflammatory agents and growth factors.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Molloy et al. teach that PDGFs have vital functions during early and intermediate stages of healing and Dunn teaches direct administration to the joint and the pharmaceutical composition for treatment of inflamed joints may comprise one or more other therapeutic agents including but not limited to anti-inflammatory agents and growth factors.

The rejection of Claims 1, 53 and 57 under 35 U.S.C. 103 (a) as being unpatentable over Lehman et al in view of Smith et al. (2002, PG PUB US 2002/0169162) is maintained.

Applicants traverse this rejection on the grounds that:

1. Lehman et al. do not teach or suggest trans-capsularly administering an inhibitor of TNF-α synthesis in the synovial fluid-containing portion of the joint.

3. Lehman et al do not teach or suggest treating an inflamed orthopedic joint

comprising trans-capsular administration of an inhibitor of TNF-α synthesis

4. Lehman et al. do not teach or suggest trans-capsularly administering an inhibitor of TNF-α synthesis through a drug pump

5. Smith et al. teaches away from administration by injection.

6. Smith et al do not teach or suggest administering an inhibitor of TNF-α synthesis either by injection or by drug pump

7. One would not be motivated to combine the teachings listed above with any reasonable expectation of success.

Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

The teachings of Lehman et al. and the relevance of these teachings to the instant application are disclosed in detail above are disclosed in detail above. Lehman does not disclose the injection of the formulation into the synovial fluid or the administration of the formulation through a drug pump. Smith et al teach an implantable sustained release device for locally administering a therapeutically effective compound to a joint (paragraph 0017), including a knee joint (paragraph 0070). The device is a mechanical one implanted intraarticularly to deliver a therapeutically effective compound within a synovial capsule of the joint (abstract). The reference teaches administration of a therapeutically effective compound to the synovial fluid of a joint (paragraph 0041). Applicants argue that Smith et al teach away from injections, but teach a device capable of releasing drugs or compounds over an extended period of time. These arguments are not persuasive because the term injection, given its broadest reasonable interpretation, could mean forcing a solution into something, i.e. pumping a therapeutic formulation into the synovial fluid of the inflamed joint. The term injection is not necessarily limited to the use of a needle and syringe, or introduction of fluid from external sources. Implantable drug delivery pumps such as morphine pumps or insulin

pumps inject therapeutic agents into the blood stream or tissue spaces. It would have been obvious to the person of ordinary skill in the art at the time the invention was made to administer a formulation comprising thalidomide as taught by Lehman et al. using the pump device disclosed by Smith et al. The person of ordinary skill in the art would have been motivated to make that modification because the art recognizes the toxic side effects of the systemic use of thalidomide and Smith et al teach that the device implanted in the joint could be used to release drugs over an extended period of time in a controlled fashion. The drugs may include anti-inflammatory drugs (paragraph 0044), which would encompass inhibitors of TNF-α synthesis. The skilled artisan reasonably would have expected success because Smith et al. teach the advantages achieved by an implantable sustained release device for locally administering a therapeutically effective compound to a joint (paragraph 0017).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Smith et al. teach the advantages achieved by an implantable sustained release device for locally administering a therapeutically effective compound to a joint.

Claim 55 is rejected under 35 U.S.C. 103 (a) as being unpatentable over Lehman et al and Dunn as applied to Claim 1 in view of Cardone et al (2003, American Family Physician, 67:2147-2152).

Applicants' traversal of this rejection and of the teachings of Lehman et al and Dunn are discussed above. Additionally, applicants assert:

1. Cardone does not teach or suggest removing a portion of the synovial fluid prior to trans-capsular administration of an inhibitor of TNF-α synthesis.

2. One would not be motivated to combine the teachings listed above with any reasonable expectation of success.

Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

The teachings of Lehman et al. and Dunn are disclosed in detail above. Lehman et al. and Dunn do not disclose removing a portion of synovial fluid prior to administration of the antagonist. Cardone et al teach a method of removing fluid from the knee joint by aspiration (page 2147, abstract, page 2151, column 2, paragraph 2). It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the method of administration of thalidomide as taught by Lehman et al. and Dunn by aspirating fluid from the knee joint prior to administration as suggested by Cardone et al. The person of ordinary skill in the art would have been motivated to make that modification because Cardone et al teach that aspiration may be performed to aid in diagnosis and relieve discomfort and one would always be motivated to relieve discomfort. The skilled artisan reasonably would have expected success because Cardone et al. teach detailed technique for performing this procedure (entire paper).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Cardone et al.

teach that aspiration may be performed to aid in diagnosis and relieve discomfort and one would always be motivated to relieve discomfort.

Claims 1 and 89 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Dunn in view of Braun et al. (2003. Expert Opin Biol Ther. 3:141-168). Dunn teaches a method of treating inflammation of an orthopedic joint by the injection (transcapsularly) of a mixture of purified growth hormone and buffer solution into the joint space (abstract, page 1) and specifically discloses treatment of a knee joint (column 1, 0001, line 5-7). The reference teaches the injection of a group of agents such as anti-cytokines (column 3, 0008, lines 45-47), which would by definition include an inhibitor of TNF-α synthesis. By way of example, Dunn discloses that the method may include the injection of Embrel, a commercially available anti-TNF agent which is a soluble TNF receptor (column 8, 0030, lines 55-56). Dunn does not specifically teach the administration of an inhibitor of TNF-α synthesis wherein the inhibitor of synthesis is a monoclonal antibody. Braun et al teaches the use of Infliximab, a chimaeric monoclonal antibody which binds to TNF-α, blocking its activity and synthesis, and effectively regulates and mediates the inflammatory process to treat rheumatoid arthritis (page 142, column 1, 2nd paragraph). Patients suffering from rheumatoid arthritis are known to exhibit inflamed orthopedic joints.

It would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to modify the method of treating an inflamed orthopedic joint taught by Dunn to administer the monoclonal antibody taught by Braun in place of the soluble TNF receptor taught by Dunn. The person of ordinary skill in the art would have been motivated to make these modifications because both Enbrel and Infliximab act to inhibit the activity of the cytokine TNF-α and reduce inflammation. One would reasonably expect success because Dunn teaches the administration of therapeutic agents, including anticytokines such as anti-TNF agents, directly to the joint to treat inflammation.

Claim 91 and 92 are rejected under 35 U.S.C. 103 (a) as being unpatentable

over Lehman and Dunn as applied to claims 1 and 49 in view of Wolfraim et al. (2004, U.S. 6,756,215, filed 19 October 2001). The teachings of Lehman and Dunn are outlined in detail above. The combined references do not teach a method of treating an inflamed orthopedic joint comprising transcapsularly administering into the joint space a formulation further comprising a growth factor wherein the growth factor is a bone morphogenetic protein (Claim 91) or wherein the growth factor is a growth and differentiation factor (Claim 92). Wolfraim et al. teach the TGF-β family of proteins include bone morphogenic proteins (BMP) and growth differentiation factors (GDF) (Column 14, lines 57-67 bridging Column 15, lines 1-9). The '215 patent teaches that this family of proteins acts to suppress inflammation (Column 15, lines 28-29) and these proteins may be used to suppress local inflammatory reactions when administered locally at various sites (Column 16, lines 4-6).

It would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to modify the method of treating an inflamed orthopedic joint taught by Lehman and Dunn to administer a formulation additionally comprising a BMP or GDF as taught by Wolfraim et al. The person of ordinary skill in the art would have been motivated to make these modifications because Dunn teaches the administration of therapeutic agents, including growth factors (growth hormone) anticytokines such as anti-TNF agents, to treat inflammation of a joint. One would reasonably expect success because Dunn teaches the administration of therapeutic agents, directly into the joint to treat inflammation of a joint.

Conclusions

Due to the new grounds of rejection herein, this action is made non final. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shulamith H. Shafer, Ph.D. whose telephone number is 571-272-3332. The examiner can normally be reached on Monday through Friday, 8 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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